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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,603	01/09/2002	Nicholas Thomas	PA-9902	7928

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AMERSHAM BIOSCIENCES
PATENT DEPARTMENT
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,603	THOMAS ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 17, 2003. Currently, claims 1-17 are pending.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims.

Priority

3. This application claims is a 371 of PCT/GB00/00807, filed March 9, 2000. The application also claims benefit of 9905807.5 filed March 12, 1999.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in United Kingdom on March 12, 1999. It is noted, however, that applicant has not filed a certified copy of the 9905807.5 application as required by 35 U.S.C. 119(b). The instant application appears to contain a foreign document, however the document does not appear to be 9905807.5. The subject matter of the application is drawn to panel form loudspeakers. The instant application is drawn to differential gene expression. Therefore, the instant application receives benefit of March 9, 2000 filing date.

Drawings

4. The drawings are acceptable.

Claim Objections

5. Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 14 appears to contain the same limitations of Claim 1d. Thus, Claim 14 no longer further limits amended Claim 1.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-17 are indefinite over the recitation "providing the nucleic aids from two sources as labeled probes wherein the nucleic acids from two sources are labeled with two different markers." It is unclear whether each of the two sources comprise two different labels, whether each sample comprises a label or whether each sample comprises the same two different labels. It is unclear whether there are two total labels

or four total labels. As written, it is unclear. Step b, of Claim 1, is unclear because it is unclear whether two reagents are required such that at least two distinguishable beads are required. The claim merely requires that any one of the pooled reagents being distinguishable from the beads of any other pooled reagent. This does not appear to require that two bead types are required, however, the claims appear to identify the beads. As written, two different bead types do not appear to be required, as argued in the response.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 6-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Beattie et al. (US Pat. 6,268,147, July 2001).

Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking

hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window (col. 39, lines 5-10). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col.

39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of color coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined rations at different levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30). Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

8. Claims 1-7, 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamb et al (WO 98/26098, June 1998).

As stated above, the claims do not appear to required two sets of beads which are distinguishable. The claim only appears to require that if there are two pooled regents, they are distinguishable.

Kamb et al. (herein referred to as Kamb) teaches a method for measuring relative amounts of nucleic acids in a complex mixture and retrieval of specific sequences. Kamb teaches detection and isolation of specific target nucleic acids from a

complex mixture of nucleic acids. The method allows quantitative comparisons of numerous individual sequences. Kamb teaches that the relative abundance of specific nucleic acids in samples derived from different sources for example from different tissue or cell types (page 10). Kamb teaches that capture oligonucleotides are attached to the surface of beads (page 11). Each bead has only one type of capture probe attached to its surface (page 12). The target nucleic acids are labeled with a marker, preferably a visual marker such as a fluorophore, to permit detection by instruments such as the automated fluorescence activated cell sorter (page 12). The target nucleic acids derived from different sources are labeled with different fluorophores which can be distinguished (page 12). The labeled target nucleic acids are pooled and contacted with a number of beads each having capture oligonucleotides of a unique sequence to form perfectly matched duplexes (page 12)(limitations of Claim 6-7). The beads are then sorted according to the relative amount of the first label and the second label and beads of interest are retrieved (limitations of Claim 14-15). Kamb teaches that mRNA or cDNA may be used as source or target polynucleotides (page 19, for example)(limitations of Claim 2-3). The attachment of capture oligonucleotides to beads includes biotinyalated DNA and avidin beads (page 51)(limitations of Claim 5). The two target nucleic acid populations are typically labeled with dyes whose emission peaks are separable with the instrument (page 41)(limitations of Claim 13).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (US Pat. 6,268,147, July 2001) in view of Cocuzza et al. (US Pat. 5,484,701, January 1996).

Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable

(detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window (col. 39, lines 5-10). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered

to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of color coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined rations at different levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30). Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

Beattie does not specifically teach immobilizing probes on beads using biotin and streptavidin-coated beads.

However Cocuzza teaches oligonucleotides may be immobilized on a bead using biotin /streptavidin-complexes. Coucuzza teaches that the biotin-avidin (streptavidin) system is a very useful analytical tool (col. 2, lines 5-8). The avidin and streptavidin form an exceptionally tight complex with biotin. Cocuzza teaches that the complexation is effectively an irreversible process 9col. 2, lines 23-25).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have immobilized the oligonucleotide probes of Beattie onto beads using the well known method of using biotin/streptavidin for immobilization taught by Cocuzza. The ordinary artisan would have been motivated to have

immobilized polynucleotides using the biotin/streptavidin system for the expected benefit of tight complexes and east of use, as taught by Cocuzza.

Conclusion

11. No claims allowable over the art.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

a) Chandler et al. (US Pat. 5,981,180, November 1999) is directed to methods of using flow cytometry to distinguish various biomolecues in real time. Chandler does not specifically teaches the use of two labeled sources.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
July 15, 2004